Rare diseases: Canada's "research orphans"

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➢ Although definitions vary by jurisdiction, diseases that affect approximately 1 in 2000 people are considered rare.[1] Canada is one of only a few developed countries without a national "orphan drug" program to protect patients with rare diseases from exorbitant drug costs. Public debate concerning government funding for these drugs is periodically stimulated by stories of patients who are deprived of life-sustaining therapies because of cost. However, most Canadians remain unaware of another important disparity between common and rare-disease care in this country: namely, the availability of research funding. Above and beyond worrying about expensive therapies, patients diagnosed with a rare disease are often surprised to learn that there is limited scientific knowledge about the causes and natural history of their condition and little or no ongoing research.

The reasons for this research gap are many. Public funding agencies have a mandate to improve public health, and so naturally favour grants that address common conditions. As a result, researchers with an interest in a rare disease who enter open grant competitions may be disadvantaged by the limited population-level impact of their potential findings.[2,3] Furthermore, the relatively small numbers of people affected by a given rare disease make it difficult for researchers to recruit and study an adequate number of patients to reach scientifically valid conclusions. As a result, even basic knowledge about the diagnosis, causes, and consequences of many of these diseases is lacking.[3] Even when these aspects are well understood and drug development can be considered, the pharmaceutical industry often opts out on the grounds that development costs are difficult to recoup from the small number of potential users of a new drug for a rare disease.[4]

In most developed nations, governments have sought to target this inequity through legislation. Since the establishment of the Office of Orphan Products Development by the US Food and Drug Administration (FDA) in 1982, various national rare disease laws, policies, and programs have been established successfully in many countries around the world.[1,5–17] Some of the most notable of these are outlined in Table 1. The impact of these programs has been significant. Since the US Orphan Drug Act was passed in the United States in 1983, over 300 rare disease products, affecting over 14 million Americans, have come to market, as compared with fewer than 10 products in the previous decade.[7] Between 2006 and 2007, the National Institutes of Health Rare Diseases Clinical Research Network produced 25 publications, posters, and abstracts, launched 24 new studies with active recruitment, and enrolled 2357 rare disease subjects.[18] The first French National Plan for Rare Diseases (2005–08) enabled the establishment of 132 "reference centres" (specialized national rare disease centres), 500 "centres of competence" (regional rare disease care providers), new best-practice guidelines for 17 rare diseases (with 24 more in preparatory stages at the time of the evaluation), and a compassionate-use system to enable orphan-drug coverage for patients.[19] The success of the European Union's rare disease research funding initiative is exemplified by the EuroBioBank. Originally funded by a seed grant of €1.22 million by the EU's fifth Framework Programme, this 10-country network of rare disease DNA, cell and tissue banks now contains 440 000 rare disease samples, among which 7000 are sent annually to researchers around the world.[20]

Patient advocacy groups have also played an important role in advancing the rare disease research agenda, both by lobbying for government action and by funding research directly. In the United States, the National Organization for Rare Disorders (NORD) (www.rarediseases.org) is a non-profit federation of over 100 volunteer organizations and 5000 patients and providers dedicated to helping people with rare diseases. The NORD website posts information about active studies along with researcher contact information for patients and their physicians (at no cost),[21] and invites applications for seed funding for the study of new treatments and diagnostic

Table 1
International initiatives to promote research and development related to rare diseases

Region	Policies / Measures	Provisions
Australia	1997 Australian Orphan Drug Program[5,6]	• Encourages rare disease drug registration and marketing by providing: — a waiver of fees for the application for orphan drug designation — a 5-year period of marketing exclusivity — technical assistance to obtain approval
European Union (EU)	1999 Regulation on orphan medicinal products	• Guarantees 10 years of market exclusivity for approved orphan products • Facilitates orphan drug registration by creating an EU-wide approval procedure • Calls for tax credits to be developed by individual member states[7,8]
	2000 Committee for Orphan Medicinal Products	• Monitors orphan-drug claims • Improves patient access to orphan drugs across the EU
	Framework Programmes (FPs) • 1998–2002: FP5 • 2002–2006: FP6 • 2007–2013: FP7	 • Funded 47 rare disease projects (€64 million) • Funded 59 projects (€230 million) • Funded over 50 projects (€237 million) between 2007 and 2010[9]
	2009 Council Recommendation on action in the field of rare diseases	• Establishes coordination among Member States to utilize national resources and expertise to reduce inequalities in access to high-quality care for rare diseases
France	2002 Rare Disease Consortium	• €7.9 million budget
	2005–08 French National Plan on Rare Diseases	• €108.5 million budget[8]
	2011–14 French National Plan on Rare Diseases[10]	• Currently actively funding projects (budget to be determined)
Germany	2003–08 Research program on rare diseases	• Funded 91 projects (€25 million)[1]
	2010 National coalition for people with rare diseases (NAMSE)	• Currently updating the German plan for rare diseases for 2011–13[11]
Japan[1]	1993 Japanese Orphan Drug Regulation	• Provides financial incentives for rare disease drug development, including: — tax incentives — fast-tracking of drug evaluation — technical assistance for drug approval — partial reimbursement of development costs — an extended registration validity period[6] — a 10-year period of exclusive marketing for successful products
Singapore	1991 Orphan Drug Act[12]	• Defines orphan drugs and the legal framework for orphan drug imports
Spain	2003 Spanish Rare Diseases Research Institute	• Promotes and carries out rare-disease clinical and basic research, provides training and support to health care providers, and funds innovation in patient care
	2003–09	• Provided funding for rare-disease research projects (€11.9 million) (2003–04)[1] • Created the first Spanish-language rare diseases information system • Included rare diseases among priority areas for the Spanish National Research Institute • Established the Centre for Biomedical Network Research on Rare Diseases (2006) • Created the State Reference Centre for Rare Diseases Patients and Families (2009)
	2009 Spanish National Health System Rare Diseases Strategy approved	• Targets medical professionals and patients with the general aim of improving health and quality of life for people with rare diseases (budget unknown)[13]
Taiwan[1]	2000 Rare Disease and Orphan Drug Act	• Covers R&D, manufacturing, and acquisition for orphan drugs and prevention, diagnosis and treatment of rare diseases, and drug subsidies • Includes a mechanism for a 70% to 100% drug and medical expense reimbursement for people with rare diseases

Table 1, continued

United States	1982 FDA Office of Orphan Products	• Promotes development of products for the diagnosis and/or treatment of rare diseases • Funds clinical research through the Orphan Products Grants Program[14] • Administers the major provisions of the Orphan Drug Act
	1983 Orphan Drug Act	• Creates financial incentives for academic institutions and manufacturers to engage in rare-disease drug development, including: — tax credits for costs of clinical research — a waiver of certain fees involved in new drug applications — direct FDA grant support — assistance for clinical research — a 7-year period of exclusive marketing for successful products[2]
	2002 Rare Diseases Act	• Provided for a new grants network for research on rare diseases • Developed regional centres of excellence for clinical research and training in rare diseases • Supports research in diagnostic tools for patients with rare diseases[15]
	2003 National Institutes of Health Rare Diseases Clinical Research Network	• Consists of a central data and technology coordinating centre with 10 disease-based research consortia[2,16] • Currently studying over 40 rare diseases at 70 sites
Multinational	2008 European Project for Rare Diseases National Plans Development (EUROPLAN)	• 30 partners (all 27 EU countries, USA, Turkey and the patient organization EURORDIS) • Ensures access to prevention, diagnosis, treatment and care through the production and dissemination of data and recommendations for developing plans or strategies for rare diseases in individual member states[17]

Note: All programs/policies without an end date are still in place.
FDA = US Food and Drug Administration

tests for rare diseases.[22] Also, it was as a result of sustained lobbying by NORD that the US Congress passed the Rare Diseases Act in 2002. In Europe, The European Organization for Rare Disorders (EURORDIS; www.eurordis.org) represents more than 260 rare disease organizations in more than 30 European countries and plays a role similar to NORD's.[23] In Canada, advocacy is provided by the Canadian Organization for Rare Disorders (CORD; www.raredisorders.ca).

In contrast to the comprehensive and proven effective approaches developed by nations around the world, Canada remains one of few countries without policies to address research into rare diseases (including drug development incentives) and drug access for patients. Since it came into existence in 2000, the Canadian Institutes of Health Research (CIHR) have seen an increase in their annual budget from around $350 million to nearly $1 billion in 2009–10.[24,25] Yet it was not until 2011 that the first funding competition specific to rare diseases was announced, allocating a maximum of $14.5 million between 2012 and 2017, including commitments from partner organizations.[26]

Logically, a comprehensive strategy to address orphan disease research should be developed and legislated at the federal level, building and improving on processes in other developed nations. For example, a caveat to the US Orphan Drug Act is that it eliminates short-term market competition by guaranteeing drug developers 7 years of market exclusivity. Although this policy has successfully driven rare disease drug development, it has also been criticized for facilitating prohibitive drug costs. In Canada, it is possible to envision a federally sponsored, single-payer system to fund pharmaceuticals for rare diseases that includes a policy mechanism that would control costs through advance negotiations with drug developers while still maintaining market incentives. Furthermore, provisions of the US Orphan Drug Act have resulted in drug development being carried out predominantly in the private sector in the United States, as opposed to government labs or universities. This should also be addressed in a future Canadian policy through specific incentives to encourage drug development in the non-profit sector.

The first step toward a Canadian policy was a Private Member's motion brought before the House of Commons in 2008 by Don Bell, then Member of Parliament for North Vancouver.[27] This motion called on the federal government to examine the feasibility of creating a Canadian Rare Disease Strategy that would emulate the principal components of the EU's strategy. Measures proposed by the motion included creating a fund for nation-wide drug coverage for rare disease sufferers, developing Canadian Centres of Reference for rare diseases, and providing public and private organizations

with incentives to undertake rare disease research, including drug development. Although the motion was passed,[28,29] no sustained debate, feasibility assessment, or measurable government action has since materialized.

A call to action

The imminent renewal of the federal-provincial Health Accord, which expires in 2014, presents an opportunity for provisions for a federally designed rare disease strategy to be tied to provincial funding, with an accountability structure to measure progress. Although the current federal government has delineated the financial terms of the future Accord, at the time of writing, discussions around national standards and provincial accountability have yet to occur.[30] To this end, the Canadian medical and scientific communities should lobby both the federal government and the CIHR directly for action. This can be achieved through free advocacy programs offered by the Canadian Medical Association (CMA), such as the MD-MP Contact Program, which matches CMA members with their local Member of Parliament. Furthermore, the CMA should prioritize this issue, presenting a unified front to the federal government. These efforts should be made in conjunction and consultation with CORD, which represents a large number of rare disease groups—a strategy that has proven to be effective in driving political change in other jurisdictions. Individual stories of rare disease sufferers being denied expensive drug coverage also routinely ignite fierce public calls for government to institute more compassionate policies. Increasing public awareness of the overarching need for a centralized rare disease policy could also stimulate an effective grassroots movement. Strategies to educate and engage the public include direct discussions with affected patients, their families, and their friends (who should be encouraged to contact their MPs), promoting activities by rare disease advocacy groups (e.g., "Rare Disease Day in Canada 2011," organized by CORD), and participating in awareness campaigns in mass-media publications and in social media (e.g., a 2011 Globe and Mail series highlighting the plight of Canadian rare disease sufferers).[31]

In the interim, or failing a federal solution, those who suffer from rare diseases and their advocates might turn to provincial governments to lead the development of rare disease programs. However, given our geographically dispersed population and the need for multicentre participation to recruit sufficient numbers of participants to rare disease studies, interprovincial partnerships for rare disease research funding, recruitment, and resource and expertise sharing will be required. Challenges include the wide range of political parties represented across provinces, their correspondingly eclectic health care priorities, and their various fiscal positions. However, these disparities would seem to pale in comparison with those between the 30 countries that have successfully instituted and currently uphold the many binding EU-wide legislative requirements and programs related to rare diseases. This suggests that a lack of political will may be the only barrier to success.

In this era of limited health care resources, a utilitarian approach to wealth distribution would argue that substantial resource investment in rare diseases fails to maximize the benefit to society by bringing the greatest good to the greatest number. However, the "paradox of rarity" is that, given the existence of over 6000 known rare diseases and the fact that 6% to 8% of the population is affected by a rare disease, even though each disease is rare, patients with rare diseases are many.[23]

Based on a belief that our society's moral obligation is to protect each individual's rights, the Canada Health Act upholds the principle of "non-abandonment,"[7] whereby all Canadians should have "timely access to health services on the basis of need, not ability to pay " and "the health care services available to Canadians are of high quality, effective, patient-centred and safe." Far beyond the simple question of access to drugs, a right to effective and high-quality care can not be fulfilled without addressing the fundamental gap in access to scientific advancement and research in rare diseases.

It is our duty to advocate for these patients by calling on our political leaders to join the rest of the developed world in legislating a comprehensive strategy to improve Canadian orphan disease care and research.

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